SmithKline Beecham
Pharmaceuticals

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Vice President and Director

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April 29, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: **[Docket No. 98D-1168] Draft Guidance for Industry -**
***ANDA's: Impurities in Drug Products* (Draft Dated December 1998)**

Dear Madam or Sir:

SmithKline Beecham Pharmaceuticals appreciates the opportunity of providing comments on the draft guidance for industry regarding impurities in drug products that are the subject of ANDAs.

Although the guidance is generally concordant with the ICH Guideline for Impurities in New Drug Products (Q3B), and such harmonization is welcome, we do have some concerns we would like to address:

1. The draft guidance document is styled on the ICH Guideline for Impurities in New Drug Products (Q3B), but it seems to make it much easier for generic companies to justify degradation product levels:

    - The approach recommended in the guidance is a comparative chromatographic study between the generic product and the reference listed drug (RLD). If the degradation products in a fresh batch of the generic product are no more than two-fold that of the RLD they are considered qualified. It seems particularly illogical to perform such a comparison on fresh batches since any meaningful comparison should be at the end of the shelf-life.

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- If the levels are two-fold or more greater than the RLD, then QSAR studies can be performed to qualify the degradation products. QSAR are not allowed for the innovator product in the existing ICH Guideline. Our Safety experts agree that the safety standards for the innovator are set higher than for generics and that the use of QSAR is an unreliable technique to assess toxicology.

- The guideline offers the advice that analytical procedures to perform this comparison may be requested from the Agency under FOI. This seems a significant advantage to offer a generic company over its competitor innovator.

2. The Introduction (Lines 3-5) states how this guidance addresses "drug products produced from chemically sythesized drug substances." It further states (Lines 22-24) that "This guidance does not apply to...fermentation products and semisynthetic products derived therefrom, herbal products, or crude products of animal or plant origin." In Lines 186-189 it then explains how one consideration for alternative Qualification Thresholds may be justified by the use of excipients "that are also crude products of animal or plant origin." If drugs of animal or plant origin are excluded from the guidance, why are they considering excipients of crude animal or plant origin? Use of the word "also" might imply that it means in addition to a drug of crude animal or plant origin. The referenced lines seem contradictory.

3. Despite the fact that semisynthetic, fermentation products are not subject to this guidance (Line 22-24), Industry is routinely being required by the Agency to provide degradation product specification and limits for these products. In fact, some of these products have been in commerce for 10 to almost 30 years without defined degradation product specs or limits for the U.S. marketed products (either regulatory or USP). If this guidance is applied, as written, to our generic competitors this would mean that while we as innovators are required to provide degradation product specifications, generics could be considered exempt from this requirement. This places the innovator at a significant disadvantage. Consequently, it would seem logical that in order to truly determine equivalence between the generic vs the innovator the degradation rate of the generic version should be examined at the end of expiry and should meet the same "end of shelf life" specifications and degradation as the innovator.

4. This comment relates to the guidelines for Qualification Procedures via Comparative Chromatographic Studies of a generic product with the Reference Listed Drug (RLD). Lines 225-234 allow qualification of a degradation product if the amount of the "identified degradation product in the generic drug product is no more than two times the amount of the corresponding degradation product in the RLD." This seems unfair to the innovator of the RLD, and we feel the rationale justifying this statement are somewhat flawed with regard to fairness: The first justification is that the RLD acceptance criteria for degradation products generally are set higher than what is observed in the RLD. This may be true but the margin between levels at end of shelf life and the product specification is not quite as wide as this "justification" implies. Innovators are typically required to set very tight limits, based on actual data at end of shelf life. The second justification is that the safety studies to qualify the RLD are carried out at significantly higher levels than the acceptance criteria. Indeed, that is the nature of safety studies, the theory being that if there is a potential safety issue it is most likely to be seen at higher levels. Also, higher levels are used to establish a clear margin of safety between the levels tested and the levels that a patient could realistically be expected to be exposed to.

   There are two ways to look at this issue: First, the RLD limits were set for a reason; to allow twice the amount of a degradation product in a generic drug product overlooks the fact that the generic could be counted on to have twice as much of the degradant at end of shelf life as well, which could well be out of specification. Or, second, the generic is only half as good as the innovator but that's good enough according to the guidance. If this is acceptable for the generic why shouldn't it acceptable for the innovator?

   We recommend that this section be reworded to allow levels of any identified degradation product to exceed the RLD by no more than 2 x SD of the assay (or within the 95% confidence interval of the assay). If the generic is going to be permitted higher levels, then so should the innovator.

5. The following observations are made with respect to Lines 87 - 99 under Section III. Identifying and Reporting Impurities:

   - The words "identify/identification" seem to be used in two contexts in this paragraph. Our interpretation is that "detection/detected" may be more appropriate in lines 87 and 91.

- We feel that a comparison of generic and RLD products by simple chromatographic retention time/response is not good science. It certainly does not "identify" degradation products (line 87) and can give spurious information for the following reasons:
  --- Excipients in RLD and generic products may be different. The chromatography may have to differ in consequence and degradation products could be "missed".
  --- Excipients may differ in RLD and generic products. This can result in different peaks and possibly different degradants, due to active-excipient interactions. It is not beyond the bounds of possibility that such "new" degradants could have the same retention times as a well-characterised degradant in the RLD product.
  --- What state is the reference RLD to be in - "Fresh" or "end of shelf life"? There is scope for confusion and "manipulation".

- The same standards ought to apply to characterisation of generic medicinal products as apply to innovator products.

- The final sentence seems overly open to interpretation. What does "substantially similar" mean? Does it mean different degradation products or different levels? Both can have safety and quality implications. A statement like "meet the same standards of quality" may be more appropriate.

- The same comments apply to "Attachment B" (which is a schematic for the approach to qualifying degradants).

6. The guideline focuses on the degradation of drug products at the time of filing an ANDA. It begins by clearly differentiating between degradation of the drug product and impurities of the drug substance. However, throughout the rest of the guideline, "impurities" and "degradation" seem to be used interchangeably. The title "ANDAs: Degradation in Drug Products" might be more accurate. (We note that the use of "impurities" terminology was also confusing in the companion ICH document (Q3B) "Impurities in Drug Products".)

   We further suggest that the Glossary better define these phrases:
   - "impurities of drug substance" - typically means process impurities of drug substance which are introduced in the primary process
   - "degradation products of drug substance"
   - "impurities of the drug product" - impurities introduced by the secondary process
   - "degradation products of drug products"

7. On the subject of individual versus total degradation, the guideline contains much information for "identifying," "reporting," and "qualifying" of individual degradation products/process impurities; these items are addressed in a similar manner in the ICH guideline. However, there is a lot of gray area on the subject of total degradation such as how to calculate it, how to set specifications, and how to extrapolate from the toxicity studies of early development batches. We recommend including a section in the guideline to better define expectations for "total degradation."

Again, we thank you for the opportunity of commenting on these issues and trust that the Agency will strongly consider these comments prior to finalizing this guidance.. If you have any questions, please contact me at (215) 751-4661.

Sincerely,

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